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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,836	06/01/2001	Shikha P. Barman	08191-018001	3677

26161 7590 04/16/2009

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/872,836	BARMAN ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,21-29,31-34 and 37* is/are pending in the application.

4a) Of the above claim(s) *5 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-16,21-24,26-29,31-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 23, 2009 that includes a response to the advisory action dated August 25, 2008, has been entered. No claims were amended, cancelled or newly added. Claims 1-16, 21-29, 31-34, and 37 are currently pending in the application. Claims 5 and 25 remain withdrawn from consideration, without traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 1-4, 6-16, 21-24, 26-29, 31-34 and 37 are under current examination.

Objection to the Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 8, line 5 of the specification). Further, an incorporation by reference by hyperlink or other form of browser executable code is not permitted. See 37 CFR 1.57(d) and MPEP § 608.01. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Response & Maintained Claim Rejections – 35 USC § 103(a)

Claims 1-4, 6-16, 29, 32-34, and 37, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos *et al.* taken with Rolland (U.S. Patent No.: 6,040,295; of record), and further in view of Lunsford (U.S. Patent Publication No.: 2002/0182258).

Claims 1-4, 6, 7, 9-16, 26, 29, 32-34, and 37, stand rejected under 35 U.S.C. 103(a) as being unpatentable over Papahadjopoulos *et al.* taken with Rolland, and further in view of Mathiowitz (U.S. Patent No.: 6,677,313). The rejections set forth pp. 5-10 of the office action dated October 6, 2005; pp. 3-5 of the office action dated February 22, 2007 and pp. 2-4 of the office action dated January 24, 2008 are maintained for reasons of record.

The teachings of the references have been summarized as follows:

The claims embrace a lipidic microparticle or lipidic microparticles comprising a PEG-DSPE, which is a polymeric matrix bound to the DSPE lipid, a plasmid vector encoding a protein or proteins of interest, and a cationic lipid/co-lipid complex. Papahadjopoulos *et al.* in column 10, second full par., states:

> It is believed that when the cationic lipid:DNA complex ("CLDC") is contacted with the hydrophilic polymer, the hydrophilic polymer locates and is incorporated into hydrophobic pockets in the complex via its hydrophobic side chains, while leaving the hydrophilic part at the exterior surface, thereby stabilizing the entire complex.

Column 10, lines 26-30 further teaches that protein based polymeric matrix can be attached to the lipidic microparticles. In addition, column 10, last par. clearly teaches that the complexes need not be provided as a liposome. As such, the complexes of Papahadjopoulos *et al.* are not encapsulated in a liposome and do not comprise a cell.

Amphiphilic cationic lipids are disclosed in details in column 11. Column 16 teaches that a targeting factor can be incorporated into the nucleic acid plasmid/cationic lipid/PEG complexes. Column 20 further teaches that the lipid:nucleic acid complexes can be administered by any of the routes normally used for introducing a molecule into ultimate contact with the blood or tissue cells. Stabilizers that can additionally employed I the complexes are disclosed in column 20, lines 32057.

With respect to the pKa recited limitation, it is acknowledged that PEG-DSPE is one of the species embraced by the lipid having a pKa of less than about 2.5. As such, and further in view of the fact that so long as the entire complex is physiologically acceptable for use in an *in vivo* environment having a physiological pH, such limitation is inherently possessed by the elected lipid PEG-DSPE and/or immaterial to the patentability of the claimed invention.

Papahadjopoulos *et al.* does not teach that the complexes can be further entrapped within polymeric microparticles with a diameter of less than about 100 microns that are used in the prior art to prolong the controlled release and bioavailability of a nucleic acid plasmid complex, nor does Papahadjopoulos *et al.* teaches explicitly that an antigenic peptide or protein encoding DNA can be used for delivery and/or expression at a desired targeted tissue such as a vagina or a mucosal tissue.

However, at the time the invention was made, Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations, *e.g.,* those formulated with a carrier or stabilizer such as a cationic polymer (abstract, entire disclosure, particularly column 1 bridging column 2, column 2, second par.. , column 3, last par bridging column 4). An addition of a targeting ligand to the microparticles and/or plasmid is also taught by Rolland so as to enhance the expression of the complexed plasmid vectors at a desired target tissue (column 2, line 45). An incorporation of stabilizer(s) and/or trafficking peptide so as to enhance transcription, translation, transcript stability, replication, and intracellular trafficking are disclosed on columns 2 and 3 as being conventional in the prior art. More importantly, Rolland teaches on columns 3 and 4 that compounds which are known to help to prolong the bioavailability of a nucleic acid, *e.g.,* protecting the nucleic acid, concentrating a nucleic acid, indirectly facilitating uptake of a nucleic acid, such as polymers, oils (a lipid based compound), surfactants can be suitably used to enhance the bioavailability of a nucleic acid.

Lunsford teaches a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized less than about 100 microns, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are delivered to a mucosal tissue such as vagina tissue, *e.g.,* pars 0055, Table 3, pars 0054, 0052, claims 36 and 37.

Mathiowitz teach a gene delivery method of employing a plurality of microparticles comprising a polymeric microparticles that are sized between one and ten microns, a stabilizer such as anhydride monomers, oligomers, organic dyes or metal compounds, and a plasmid DNA coding for a protein of interest such as an antigenic polypeptide, wherein the microparticles are

delivered to a mucosal tissue such as vagina tissue, *e.g.,* see column 2, lines 17-56, column 4, last par., columns 7 and 8, and columns 12 and 13. Plasmid vectors including a targeting ligand is disclosed on column 19, lines 21-23.

Applicants traverse the rejection and argue that the Advisory Action does not appear to maintain the original basis for rejection, by stating that: "[a] person of ordinary skill in the art would not need to incorporate the components of the microparticle of Papahadjopoulos et al., into those of Lunsford or Mathiowitz. Rather the references of Lunsford and Mathiowitz were used to supply the deficiencies in Papahadjopoulos et al. relating to microparticle diameter and antigenic peptide for delivery to mucosal tissue." Because such is at odds with the basis for rejection in the previous office actions, i.e. that "it would have been obvious for one of ordinary skill in the art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos et al." Further arguing that it is Applicants'' understanding that the Examiner no longer maintains this previous rejection. Applicants' arguments have been fully considered, but are not found to be persuasive.

In response, it should be noted that the Examiner does not consider the previous statements to be at odds, because the Advisory action indicates that bodily incorporation of the components of the microparticle of Papahadjopoulos et al. into those of Lunsford or Mathiowitz is not required. Such is consistent with the original basis that the known polymeric microparticles of Lundsford may be used by a person of ordinary skill in the art to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos et al. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicants argue that the Advisory Action contains no assertion as to any reason why a person of ordinary skill in the art would have modified a composition of Papahadjopoulos to include features of the compositions of Lunsford and Mathiowitz relating to microparticle

diameter and antigenic peptide for delivery to mucosal tissue, and therefore the rejection does not establish a *prima facie* case of obviousness.

Such is not found persuasive, because the Advisory Action simply responded to Applicants' arguments. There is no requirement for the Advisory Action to re-iterate the detailed reasons for the rejection, that have already been made of record.

As previously indicated, it would have been a *prima facie* obvious for one of ordinary skill in art to employ known polymeric microparticles such as those disclosed in Lunsford to entrap and enhance the stability of the lipid:nucleic acid:PEG-DSPE complexes of Papahadjopoulos *et al.* One of ordinary skill in the art would have been motivated to employ polymeric microparticles having a size of less than 100 microns in diameter, in the complexes of Papahadjopoulos *et al.* because Rolland teaches that not only polymeric microparticles can be used to enhance and prolong the bioavailability of naked plasmid vectors encoding a product of interest, the microparticles can also be used to do the same with nucleic acid plasmid vectors presented in various formulations. One also would have been motivated to do so in order to enhance the controlled release of the lipidic:nucleic acid complexes of Papahadjopoulos *et al.* and protect the plasmid vectors from degradation during its circulation *in vivo.*

Applicants argue that Papahadjopoulos differs from the claimed microparticles in at least the following respects: (1) there is no indication in Papahadjopoulos that a hydrophilic polymer described therein forms a "polymeric matrix" in the reference's cationic lipid:nucleic acid complexes; (2) Papahadjopoulos does not disclose a composition containing a polymeric matrix and a lipid having a pKa of less than about 2.5; and (3) Papahadjopoulos does not disclose a non-liposome composition that is less than about 100 microns in diameter. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Papahadjopoulos et al., disclose lipidic microparticles linked to targeting moieties (Abstract), prepared by contacting a nucleic acid with an organic polycation and an amphiphilic cationic lipid and then combining the complex thus formed with a hydrophilic polymer, that may

be PEG-DSPE (columns 3 and 4 bridging). The reason for inclusion of a hydrophilic polymer and PEG-DSPE in the microparticle is expressly provided by the primary reference. The cationic lipid nucleic acid microparticles of Papahadjopoulos et al. comprise hydrophilic polymers and PEG-DSPE condensed with organic polycations. Polymeric matrices are described by Lunsford et al. The claimed pKa value is inherent to the PEG-DSPE described by Papahadjopoulos et al. Papahadjopoulos et al. clearly teach that "the lipids need not be provided as a liposome." (column 10). They further state: "It is also recognized that after complexation, the lipid:nucleic acid complex may no longer exist as a true vesicle and therefore is not generally regarded as a liposome." (column 10). As such, the microparticles of Papahadjopoulos *et al.* are not encapsulated in a liposome and do not comprise a cell. Moreover, Lunsford et al. state that the lipids can be cationic and preferably are not present as liposomes that encapsulate the microparticles. The lipids may optionally form micelles (paragraph [0127]). With regard to microparticle diameter, Lunsford discloses polymeric matrix microparticles having a diameter less than about 100 microns (Abstract). Note that the microparticles of different sizes of less than 100 microns are routinely made in the prior art by filtering and/or emulsion/mixing techniques, given the disclosure of Lunsford, and particularly since the size limitation does not appear to contribute any inventive feature to the invention. Applicants are reminded that for the purpose of combining references under 35 U.S.C. 103(a), the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Further, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988).

Applicants argue that in contrast to Papahadjopoulos's lipid:nucleic acid complexes, Lunsford and Mathiowitz describe polymeric microparticles. Given the fundamental structural differences between the lipid:nucleic acid complexes of Papahadjopoulos and the polymeric microparticles of Lunsford and Mathiowitz, the skilled person would have had no reason to have made the modifications now suggested by the Examiner. Such is not found persuasive, because Applicants appear to have ignored the teachings of Papahadjopoulos et al. that are directed to

lipidic microparticles (emphasis added; see Title and Abstract). Thus, the teachings of Papahadjoupoulos et al. Lunsford et al. and Mathiowitz et al. are each directed to microparticles for delivery of nucleic acids.

Claims 21-24, 26-28, and 31 stand rejected under 35 USC 103(a) as being unpatentable over Lunsford (U.S. Patent Publication No.: 2002/0182258), in view of Papahadjopoulos et al. (U.S. Patent No. 6,803,053). The rejection set forth on pp. 4-5 of the final office action dated January 24, 2008 is maintained for reasons of record.

The claims embrace a lipidic microparticle less than 100 microns or less than 50 microns, or lipidic microparticles comprising a PEG-DSPE (a lipid phosphonate) and a polymeric matrix, wherein the microparticle is not encapsulated in a liposome, a nucleic acid molecule encoding a peptide having a length and sequence that permit it to bind to an MHC class I molecule, and a method of administering said microparticle to an animal.

The teachings of the references have been summarized as follows:

Lunsford et al. disclose a preparation of microparticles for delivery of nucleic acids comprising a polymeric matrix, a nucleic acid expression vector, and a lipid, wherein the microparticles have a diameter less than about 100 microns (Abstract and Title). The microparticle may be less than 20 microns (claim 1), and the nucleic acid of the microparticle may comprise an expression control sequence operatively linked to a coding sequence (claim 4) that is a peptide having a length and sequence which permit it to bind to an MHC class I molecule (claim 8(c)). The encoded polypeptide may consist of at least two peptides linked in tandem, wherein the at least two peptides are not identical (claim 14), or are overlapping (claim 15), or are immunogenic (claim 18). The microparticles are further disclosed in a method of administering nucleic acid to an animal (claim 51).

While Lunsford et al. do not specifically disclose the lipid of the microparticle as PEG-DSPE, they state that the lipid may be a cationic lipid (claim 9) or a phospholipid (claim 11), thus providing the motivation to incorporate any cationic lipid or phospholipids in their polymeric matrix to form a microparticle.

Papahadjopoulos *et al.* disclose lipidic microparticles linked to targeting moieties (Abstract), prepared by contacting a nucleic acid with an organic polycation and an amphiphilic cationic lipid and then combining the complex thus formed with a hydrophilic polymer, that may be PEG-DSPE (columns 3 and 4 bridging). Papahadjopoulos et al. clearly teach that "the lipids need not be provided as a liposome." (column 10). They further state: "It is also recognized that after complexation, the lipid:nucleic acid complex may no longer exist as a true vesicle and therefore is not generally regarded as a liposome." (column 10). As such, the microparticles of Papahadjopoulos *et al.* are not encapsulated in a liposome and do not comprise a cell. With respect to the recited limitation of lipid pKa, the pKa associated with PEG-DSPE is a property inherently possessed by the lipid and is immaterial to the patentability of the claimed invention.

Thus, at the time of the instant invention it would have been *prima facie* obvious for one of ordinary skill in the art to include PEG-DSPE disclosed by Papahadjopoulos *et al.* in the microparticle of Lunsford et al., with a reasonable expectation of success, to produce the microparticle of the instantly claimed invention. One of ordinary skill in the art would have been motivated to utilize PEG-DSPE as a lipid in the polymeric matrix composition of Lunsford et al., because the inclusion of polymers and phospholipids was expressly provided for by Lunsford et al.

Applicants traverse the rejection, arguing that the exemplary "cationic lipids" listed by Papahadjopoulos (at column 11, lines 6-7) include DODAC, DOTMA, DDAB, DOTAP, DC-Chol, and DMRIE; and nowhere does Papahadjopoulos suggest that PEG-DSPE can or should be used as the cationic lipid component in its complexes. Applicants concluding, even if a person of ordinary skill in the art were to select a "cationic lipid" component disclosed by Papahadjopoulos and use that cationic lipid as the cationic lipid in a microparticle composition of Lunsford, such a modification would not result in the claimed compositions. Applicants additionally arguing that Papahadjopoulos describes PEG-DSPE as an example of the "hydrophilic polymer" component of its complexes (i.e., not as an example of the "cationic lipid" component) and states that PEG-DSPE can be included in its complexes as a means to prevent aggregation of the complexes and thereby enhance their shelf life, and would have been irrelevant in the polymeric microparticles of Lunsford. Applicants' arguments have been fully considered, but are not found persuasive.

As previously indicated, Lunsford et al. do not limit the lipid components of their microparticle to a cationic lipid. In paragraph [0043], page 6, Lunsford et al. state that the lipid can be, e.g, a cationic lipid, an anionic lipid, or a zwitterionic lipid, or may have no charge. Examples of lipids include cetyltrimethylammonium and phospholipids. The fact that Papahadjopoulos et al. exemplify PEG-DSPE as a hydrophilic polymer to be included in their microparticles, does not negate the fact that it is additionally a phospholipid. Further, the ability of PEG-DSPE to enhance shelf life of the formed complex, provides additional motivation for its inclusion in Lunsford et al.'s microparticles.

Thus, the rejections are maintained for reasons of record and the foregoing commentary.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633